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## Original article

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# Association of serum C-reactive protein and erythrocyte sedimentation rate with muscle strength in patients with knee osteoarthritis

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## Abstract

**Objective.** To examine the association of serum CRP and ESR with muscle strength in patients with knee OA.

**Methods.** Cross-sectional data from 285 patients with knee OA from the Amsterdam Osteoarthritis (AMS-OA) cohort were analysed. CRP (mg/l) and ESR (mm/h) were measured in serum from patients' blood samples and the values were dichotomized for the analyses. Strength of quadriceps and hamstring muscles was assessed using an isokinetic dynamometer. Univariable and multivariable linear regression analyses were used to assess the association of CRP and ESR with muscle strength, adjusting for relevant confounders.

**Results.** Elevated levels of serum CRP ( $\beta = -0.10$ ;  $P = 0.04$ ) and ESR ( $\beta = -0.12$ ;  $P = 0.02$ ) were associated with lower muscle strength after adjustment for age, sex, comorbidities and NSAID use. The associations were no longer significant when BMI was incorporated in the adjusted model.

**Conclusion.** Inflammation might influence muscle strength in patients with knee OA. Moreover, the link between inflammation and obesity might explain the effect that BMI has in the associations between inflammatory markers (i.e. CRP and ESR) and muscle strength.

**Key words:** knee osteoarthritis, inflammatory markers, C-reactive protein, erythrocyte sedimentation rate, muscle strength.

## Introduction

OA is a highly prevalent disease that has been associated with decreased muscle strength and activity limitations [1, 2]. Even though OA has traditionally been considered a non-inflammatory disease compared with RA, evidence

has recently shown a low grade of inflammation mainly associated with synovitis in this group of patients [3–6]. However, in contrast to patients with well-known inflammatory diseases like RA in which inflammatory markers such as CRP and ESR are usually elevated, in patients with OA only slight or moderate elevations of inflammatory markers (i.e. CRP and ESR) have been described [7–11].

Previous studies have analysed the relationship of CRP and ESR values with pain, global severity/progression of the disease and activity limitations in patients with OA [9, 10, 12, 13]. Moreover, ESR but not CRP was inversely correlated with hand grip strength ( $P < 0.005$ ) [10]. However, there are still scarce data on the association of these inflammatory markers and muscle strength in this group of patients. In older adults and in patients with RA, increased circulating levels of inflammatory cytokines, such as IL-6 and TNF- $\alpha$ , have been associated with sarcopenia and muscle weakness [14–17]. Further

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evidence has suggested that elevated levels of circulating inflammatory markers (i.e. cytokines) might be involved in muscle atrophy and impaired muscle regeneration in older adults [18, 19]. In patients with OA, a recent study has reported a relationship between elevated markers of inflammation (IL-6) in vastus lateralis biopsies and knee muscle weakness (extensors and flexors) [20]. In contrast, using plasma inflammatory markers (IL-6), inflammation and knee extensor strength were not associated in this group of patients [21]. In conclusion, the relationship between inflammation and muscle strength has hardly been studied in patients with OA, and the results have been conflicting.

Based on the hypothesis that inflammation might explain some of the decrease in muscle strength that is usually found in patients with OA, the purpose of this cross-sectional study was to examine the association of serum inflammatory markers (i.e. CRP and ESR) with muscle strength in patients with established knee OA.

## Patients and methods

### Subjects

Two hundred and eighty-five participants from the Amsterdam Osteoarthritis (AMS-OA) cohort (179 females, 106 males) with unilateral or bilateral diagnosis of knee OA according to the ACR [22] were included in this study [23]. The AMS-OA is a cohort of patients with OA of the knee and/or hip according to the ACR criteria [22, 24], who have been referred to an outpatient rehabilitation centre (Reade, Centre for Rehabilitation and Rheumatology, Amsterdam, the Netherlands). Participants were assessed by rheumatologists, radiologists and rehabilitation physicians. Total knee replacement, RA or any other form of inflammatory arthritis (i.e. crystal arthropathy, septic arthritis, SpA) were considered exclusion criteria. Demographic, radiographic, biomechanical, clinical and psychosocial factors related to OA were assessed. All the participants provided written informed consent according to the Declaration of Helsinki. The study was approved by the Slotervaart Hospital/Reade Institutional Review Board.

### Measures

#### *Inflammatory markers*

Inflammatory markers were measured in serum from patients' blood samples. CRP (mg/l) was processed immunoturbidimetrically using CRPLX test kits [25, 26] and the Roche Cobas-6000 analyser (Roche Diagnostics GmbH, Mannheim, Germany). ESR values were determined by the standard Westergren method [27]. In this method, EDTA anti-coagulated blood samples were pre-diluted with saline solution and aspirated into the Westergren pipette graduated from 0 to 200 mm. The rate at which red blood cells sedimented in 1 h was measured and reported in mm/h.

#### *Muscle strength*

Knee muscle strength was assessed using an isokinetic dynamometer (EnKnee, Enraf-Nonius, Rotterdam, the

Netherlands) [28]. An initial practice attempt was used for the patients to get familiar with the required movements. The patients performed three maximal test repetitions to measure the isokinetic strength of the quadriceps and hamstrings for each knee, at 60°/s. Mean quadriceps and hamstring muscle strength per leg was calculated (in Nm), and divided by the patient's weight (in kg) [23, 29]. This measurement (in Nm/kg) has shown excellent intra-rater reliability [intraclass correlation coefficient (ICC) 0.93] in knee OA patients [30].

#### *Potential confounders*

Demographic data (i.e. age and gender) were recorded. Information related to comorbidities was collected with the Chronic Illness Rating Scale [31]. This instrument allows the gathering of information related to 13 body systems, scoring from 0 (none) to 4 (extremely severe) according to the severity of the condition. The number of diseases on which the patients scored a severity of  $\geq 2$  was calculated and incorporated in the analyses. NSAID use was dichotomized (yes, no) if the patients were taking NSAID medicines or not. BMI was calculated as body mass in kilograms divided by height in squared metres ( $\text{kg}/\text{m}^2$ ).

### Statistical analysis

Descriptive statistics were used to characterize the study population. Percentages were used for categorical variables, means (s.d.s) and medians [inter-quartile ranges (IQRs)] for continuous variables. Linear regression analyses were used to analyse the association of inflammatory markers (CRP and ESR) as independent factors with muscle strength (Nm/kg) as dependent factor. CRP was dichotomized as 0 if levels in serum were low to intermediate ( $\leq 3$  mg/l) and 1 if levels were elevated ( $> 3$  mg/l). This cut-off level was chosen according to previous studies in patients with OA [11, 32]. A sensitivity analysis using CRP cut-off point of 2 mg/l was carried out (data not shown). ESR was dichotomized following the classification criteria of low to normal rate 0 ( $< 20$  mm/h) and elevated rate 1 ( $\geq 20$  mm/h) [24].

First, regression analyses were used to analyse the association of CRP and ESR with muscle strength (crude models). Secondly, single confounding effects of potentially relevant variables (i.e. age, gender, comorbidities, NSAID use and BMI) were determined (Table 1). Thirdly, multivariable regression models adding one relevant confounding variable at a time were analysed (Table 2). Statistical significance was accepted at  $P < 0.05$ . All analyses were performed using SPSS software, version 18.0 (SPSS, Chicago, IL, USA).

## Results

### Descriptives

Almost two-thirds (63%) of the group ( $n = 179$ ) were women and the mean (s.d.) age was 61.7 (7.3) years. The median (IQR) of CRP and ESR in the study group was 2 mg/l (2–4) and 9 mm/h (4–15), respectively. A total of 26% of the study population had CRP levels  $> 3$  mg/l

**TABLE 1** Associations of CRP and ESR with muscle strength in patients with knee OA ( $n=285$ )

Independent factors	Muscle strength, Nm/kg	
	$\beta$	$P$ -value
CRP	-0.13	0.03
CRP + age <sup>a</sup>	-0.15	0.02
CRP + gender <sup>a</sup>	-0.09	0.07
CRP + comorbidities <sup>a</sup>	-0.14	0.02
CRP + NSAID <sup>a</sup>	-0.12	0.05
CRP + BMI <sup>a</sup>	0.01	0.81
ESR	-0.21	<0.001
ESR + age <sup>a</sup>	-0.21	<0.001
ESR + gender <sup>a</sup>	-0.13	0.01
ESR + comorbidities <sup>a</sup>	-0.21	0.001
ESR + NSAID <sup>a</sup>	-0.20	0.001
ESR + BMI <sup>a</sup>	-0.07	0.22

Linear regression analysis using muscle strength as dependent factor. <sup>a</sup>Adjusted models.

**TABLE 2** Association of CRP and ESR with muscle strength in patients with knee OA in multivariable analyses ( $n=285$ )

Independent factors	Muscle strength, Nm/kg	
	$\beta$	$P$ -value
CRP	-0.13	0.03
CRP <sup>a,b</sup>	-0.11	0.03
CRP <sup>a,b,c</sup>	-0.11	0.03
CRP <sup>a,b,c,d</sup>	-0.10	0.04
CRP <sup>a,b,c,d,e</sup>	0.04	0.44
ESR	-0.21	<0.001
ESR <sup>a,b</sup>	-0.13	0.01
ESR <sup>a,b,c</sup>	-0.12	0.02
ESR <sup>a,b,c,d</sup>	-0.12	0.02
ESR <sup>a,b,c,d,e</sup>	0.02	0.67

Linear regression analysis using muscle strength as dependent factor. Crude model adjusted for <sup>a</sup>age, <sup>b</sup>gender, <sup>c</sup>comorbidities, <sup>d</sup>NSAID and <sup>e</sup>BMI.

( $n=73$ ), with a mean (s.d.) of 7.41 (7.34) mg/l. ESR was  $\geq 20$  mm/h in 18% of the patients ( $n=51$ ), with a mean (s.d.) of 27.00 (7.83) mm/h. In the non-elevated CRP and ESR groups the mean (s.d.) were 1.62 (0.83) mg/l and 7.90 (4.73) mm/h, respectively. The mean (s.d.) muscle strength of the study population was 0.9 (0.4) Nm/kg. Further demographic and clinical characteristic data are shown in Table 3.

#### Association of inflammatory markers (CRP and ESR) with muscle strength

The relative symmetry of distribution of muscle strength according to elevated or non-elevated inflammatory markers are presented in the Figs 1 (CRP) and 2 (ESR).

**TABLE 3** Baseline characteristics ( $n=285$ )

Age, years <sup>a</sup>	61.7 (7.3)
Female, $n$ (%)	179 (63)
Knee muscle strength, Nm/kg <sup>a</sup>	0.9 (0.4)
Comorbidities (CIRS $\geq 2$ ), $n$ (%)	
0	145 (50.9)
1	68 (23.9)
2	45 (15.8)
$\geq 3$	25 (8.8)
Missing	2 (0.7)
NSAID use (yes), $n$ (%)	40 (14)
BMI <sup>a</sup> , kg/m <sup>2</sup>	29.3 (5.6)
Radiographic OA <sup>b</sup> K/L score $\geq 2$ , $n$ (%)	193 (67.7)
Inflammatory markers, median (IQR)	
CRP, mg/l	2 (1–4)
ESR, mm/h	9 (4–15)

<sup>a</sup>Mean (s.d.); <sup>b</sup>Highest knee score. K/L: Kellgren–Lawrence; CIRS: Chronic Illness Rating Scale.

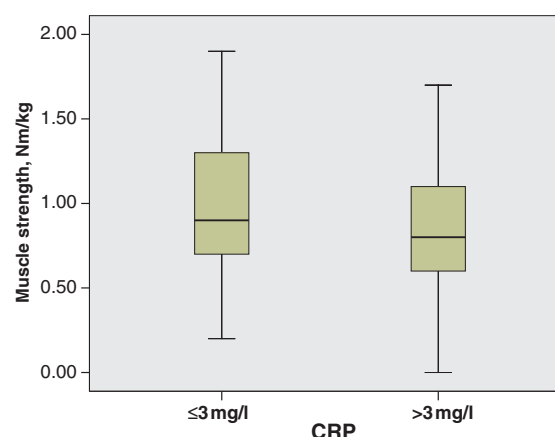
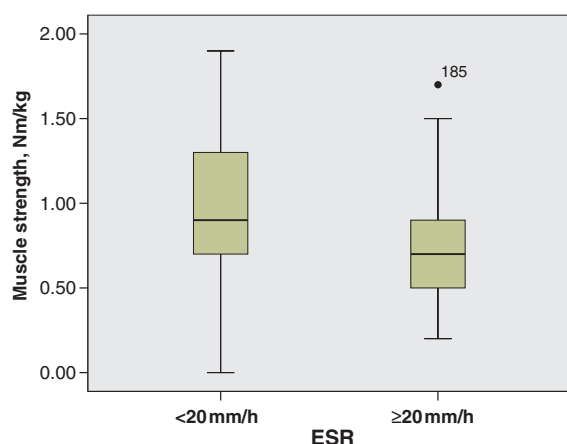
**Fig. 1** Distribution of CRP and muscle strength in patients with knee OA.

Table 1 shows the crude association of CRP and ESR with muscle strength. Elevated CRP (crude  $\beta = -0.13$ ;  $P = 0.03$ ) and ESR (crude  $\beta = -0.21$ ;  $P < 0.001$ ) values were significantly associated with lower muscle strength. Simple adjusted models analysed the influence of each potential confounder (i.e. age, gender, comorbidities, NSAID use and BMI) at the time. In these simple models, gender and BMI were the factors that most affected the crude models.

In the multivariable regression models, one relevant confounding variable was added at a time (Table 2). Elevated values of CRP ( $>3$  mg/l) ( $\beta = -0.10$ ;  $P = 0.04$ ) and ESR ( $\geq 20$  mm/h) ( $\beta = -0.12$ ;  $P = 0.02$ ) were still associated with lower muscle strength after adjustment for age, gender, comorbidities and NSAID use. However, the associations between inflammatory markers and muscle strength were no longer significant (CRP  $\beta = 0.04$ ;  $P = 0.44$  and ESR  $\beta = 0.02$ ;  $P = 0.67$ ) when BMI

**Fig. 2** Distribution of ESR and muscle strength in patients with knee OA.



was added to the models. A sensitivity analysis with CRP cut-off point of 2 mg/l yielded the same conclusion (data not shown).

## Discussion

This study investigated the association of serum inflammatory markers (i.e. CRP and ESR) with muscle strength in a group of patients with knee OA. We found that, in patients with OA, elevated serum inflammatory markers (i.e. CRP >3 mg/l and ESR ≥20 mm/h) were associated with lower knee muscle strength. Previous studies have clearly documented the relationship between elevated inflammatory markers and muscle weakness in patients with RA [14, 33] and in older adults [15, 17]. However, except for Wolfe [10] who previously studied the correlation of ESR and CRP with hand grip strength in patients with knee and hip OA, to the best of our knowledge this is one of the first studies that described the association between serum inflammatory markers (i.e. CRP and ESR) and muscle strength in patients with established diagnosis of knee OA.

The results of the present study are consistent with Levinger *et al.* [20] who previously reported an association between inflammation (IL-6) and knee muscle weakness (extensors). However, the previous study was highly invasive as it used inflammatory markers from muscle biopsies. It was carried out in a small population ( $n = 19$ ) and its results were not controlled for relevant confounders. On the other hand, Santos *et al.* [21] did not find a significant correlation between inflammatory markers in plasma (IL-6) and knee muscle strength (extensors and flexors) in a group of females with knee OA ( $n = 80$ ). In contrast to previous studies, in the present study serum inflammatory markers that can be easily obtained in clinical practice were analysed in a larger population of patients with knee OA ( $n = 285$ ). Even after adjustment for relevant confounders (i.e. age, sex, comorbidities and NSAID use) our results showed statistically significant associations. As far

as we know, this is the largest study suggesting inflammation as a possible factor influencing knee muscle strength in this group of patients.

The relationship found between elevated inflammatory markers and lower muscle strength is coherent with findings of previous studies carried out in the general elderly population, in which elevated levels of inflammatory markers were associated not only with lower muscle strength, but also with loss of muscle mass and sarcopenia [15, 17]. These associations might be explained by the catabolic effect of inflammatory markers on muscle tissue [34], and their possible influence on the decrease in muscle regenerative potential [18]. Results from studies carried out in rats suggested that inflammatory factors might cause muscle breakdown [35, 36]. Moreover, Bodell *et al.* [37] indicated that long exposure of skeletal muscle to IL-6 can retard muscle growth in rats, possibly due to the interaction with key growth factors. Although these mechanisms have not been intensively studied in humans, the same mechanism as found in rat models might be involved in the development of muscle weakness in humans.

Muscle strength was more strongly associated with ESR ( $P < 0.001$ ) than with CRP ( $P = 0.03$ ). A possible explanation might be the longer half-life of ESR in the system compared with the rapid changes in concentration of CRP. Although CRP and ESR are considered non-specific tests, their values can contribute to the detection of diverse conditions associated with inflammation. Both ESR and CRP are commonly used as markers of acute-phase response of inflammation. However, CRP is more sensitive than ESR to changes in the onset of acute-phase response, increasing rapidly within hours of the stimulus, and then returning to normal values following resolution.

After incorporating BMI to the adjusted model, the associations of CRP and ESR with muscle weakness were no longer significant. Obesity, a primary risk factor for OA of the knee, has been associated with a condition of low-grade inflammation that may contribute to progressive joint degeneration [38, 39]. This relationship might be explained by the possible production and secretion of several pro-inflammatory cytokines by the adipose tissue [40]. Another possible explanation may be associated with the non-hepatic production of CRP through the stimulation of adiposities by inflammatory cytokines [41]. Previous studies have found a strong association between systemic inflammatory markers and BMI [32, 42]. Moreover, BMI has been reported as an important mediator in associations between CRP and ESR, and various clinical characteristics in OA patients [32, 42, 43]. Due to the link between obesity and inflammatory markers, the adjustment of the associations for BMI might result in an overcorrection of the model.

Some limitations to this study have to be considered. First, with the cross-sectional design of the present study we can only probe that associations exist, but it is not possible to establish the causality underlying them. Based on previous literature, we hypothesized that elevated levels of inflammatory markers contribute to



muscle weakness. However, longitudinal studies should be undertaken to prove this hypothesis. Secondly, although some relevant confounders were included, the level of physical activity of the patients was not considered. As some studies have documented the positive effect of physical activity in reducing the levels of inflammatory markers [44], it is possible that the associations found in this study might be modified if the level of physical activity of the participants were considered. A key strength of our study is the use of serum inflammatory markers that can be easily obtained in clinical practice from a blood sample. Another strength of this study is the large number of patients with knee OA ( $n = 285$ ) studied compared with previous studies related to inflammatory markers and knee muscle strength [20, 21].

From a clinical perspective, given the relationship between muscle strength and activity limitation in patients with knee OA [2], the results of this study imply that, theoretically, controlling inflammation and reducing overweight in patients with knee OA might contribute to better results in rehabilitation programmes, adding to the improvement of muscle strength and subsequent decrease in activity limitation. Nevertheless, intervention research is needed to prove this hypothesis.

In conclusion, in patients with knee OA, elevated levels of serum CRP and ESR were associated with lower knee muscle strength. Moreover, the link between inflammation and obesity might explain the effect that BMI has in the association of inflammatory markers (i.e. CRP and ESR) with muscle strength.

#### Rheumatology key messages

- Elevated CRP and ESR were significantly associated with lower muscle strength in patients with knee OA.
- BMI might influence the association between inflammatory markers and muscle strength in knee OA.

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